



Separation of ^{90}Y Microspheres and Imaging with PET/CT: Phantom Study

^{90}Y Mikrosferlerinin Ayrılması ve PET/BT ile Görüntülenmesi: Fantom Çalışması

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Abstract

Objectives: Yttrium 90 (^{90}Y) microspheres are utilized in the treatment of liver tumors. This study aimed to prepare ^{90}Y suitable for experimental studies by separating it from within the microspheres and imaging it cartographically in positron emission tomography/computed tomography (PET/CT).

Methods: ^{90}Y microspheres were incubated for 2 hours in a solution containing 5.5 molar sodium chloride (NaCl) and 6 molar hydrochloric acid at pH 5. After this period, separation was achieved by passing through a 0.22 μm pore size polytetrafluoroethylene filter. A liver phantom, mimicking human liver equivalent dimensions and containing two simulated tumors, was filled with ^{90}Y and imaged scintigraphically in PET/CT.

Results: The true ^{90}Y ratios between the large simulated tumor and the small simulated tumor compared to normal liver tissue were approximately 10:1 and 2:1, respectively. PET/CT images yielded these ratios as 11.3 and 2.13 for the large and small tumors, respectively. Homogeneous distribution of ^{90}Y within the simulated liver tissue was observed.

Conclusion: The separation technique enabled preparation of a homogeneous ionic ^{90}Y solution suitable for quantitative PET/CT phantom imaging and may facilitate future phantom-based dosimetric studies.

Keywords: Yttrium 90 (^{90}Y), microspheres, separation processes, PET/CT imaging

Öz

Amaç: İtiryum-90 (^{90}Y) mikroküreler karaciğer tümörlerinin tedavisinde kullanılmaktadır. Bu çalışmanın amacı, ^{90}Y 'yi mikrokürelerden ayırarak deneysel çalışmalara uygun hale getirmek ve pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) ile kartografik olarak görüntülemektir.

Yöntem: ^{90}Y mikroküreler, pH 5'te 5,5 molar sodyum klorür (NaCl) ve 6 molar hidroklorik asit içeren bir çözelti içerisinde 2 saat inkübe edildi. Bu sürenin ardından, 0,22 μm gözenek çapına sahip politetrafluoroetilen filtreden geçirilerek ayırma işlemi gerçekleştirildi. İnsan karaciğerine eşdeğer boyutları taklit eden ve iki simüle tümör içeren bir karaciğer fantomu ^{90}Y ile dolduruldu ve PET/BT'de sintigrafik olarak görüntüldü.

Bulgular: Büyük simüle tümör ve küçük simüle tümörün normal karaciğer dokusuna kıyasla gerçek ^{90}Y oranları sırasıyla yaklaşık 10:1 ve 2:1 olarak belirlendi. PET/BT görüntülerinde bu oranlar büyük ve küçük tümörler için sırasıyla 11,3 ve 2,13 olarak elde edildi. Simüle karaciğer dokusu içerisinde ^{90}Y 'nin homojen dağılım gösterdiği gözlemlendi.

Sonuç: ^{90}Y mikroküre kompleksinden elde edilen saflaştırılmış ^{90}Y çözeltisi, deneysel çalışmalarda kullanılabilecek bir forma dönüştürülmüştür.

Anahtar Kelimeler: İtiryum-90 (^{90}Y), mikrosferler, ayırım işlemleri, PET/BT görüntüleme

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Introduction

Selective internal radiation therapy using yttrium-90 (^{90}Y)-loaded microspheres is an effective treatment modality for liver tumors. In this method, high radiation doses are delivered directly to the tumor via the hepatic artery using catheter-based techniques (1,2,3,4,5). Radioembolization is a targeted technique involving the administration of ^{90}Y -containing microspheres into specific branches of the hepatic artery. After intrahepatic arterial infusion, ^{90}Y microspheres become trapped within the microvascular bed. When ^{90}Y decays, it emits beta (β) radiation with an average energy of 0.93 MeV and a maximum energy of 2.26 MeV. Electrons at these energies can generate Bremsstrahlung (deceleration X-rays) when interacting with tissue. Gamma camera imaging utilizes these X-rays. In addition, ^{90}Y emits low-yield annihilation photons at a rate of approximately 32 per million decays, enabling positron emission tomography (PET) imaging (6).

In liver tumor treatment, two commonly used dosimetry approaches exist: pre- and post-treatment dosimetry.

Pre-treatment dosimetry is performed using $^{99\text{m}}\text{Tc}$ -MAA-based scintigraphic imaging with a gamma camera. The first step in dosimetric calculations is the determination of the lung shunt fraction, which reflects the fraction of activity shunted from the liver to the lungs. In addition, the radiation tolerance of normal liver tissue and the intended tumor absorbed dose can be calculated for treatment planning (7,8,9,10). After calculations performed with $^{99\text{m}}\text{Tc}$ -MAA, the determined dose is administered to the patient using ^{90}Y microspheres (11). It is well known that the intrahepatic distribution of $^{99\text{m}}\text{Tc}$ -MAA microspheres differs from that of ^{90}Y microspheres. Therefore, post-treatment dosimetric studies using ^{90}Y microspheres are also performed (12,13). For this purpose, some studies have used phantoms simulating the human liver and lungs labeled with ^{99}Tc (14). However, due to technical limitations, no pre-dosimetric phantom studies using ^{90}Y microspheres have been reported. In contrast, post-dosimetric studies using ^{90}Y microspheres in patient imaging do exist. One such study was performed by D'Arienzo et al. (15) using a phantom with ^{90}Y chloride. In that study, ^{90}Y was used in chloride form without microspheres, allowing a homogeneous distribution of ^{90}Y in PET/computed tomography (CT) imaging and enabling dosimetric analysis.

Partial volume effect (PVE) is a phenomenon that complicates scintigraphic differentiation in small liver tumors, as in all nuclear medicine imaging. PVE is a complex process influenced by several factors, including tumor size and shape, background activity in surrounding tissues,

spatial resolution of the imaging system, voxel size, and imaging modality. Chiesa et al. (16) reported that lesions smaller than 3 cm are affected by PVE, and particularly tumors smaller than 2 cm cannot be reliably corrected for PVE and therefore should be excluded from evaluation. These investigators studied PVE both in phantoms and in patients using $^{99\text{m}}\text{Tc}$. Further phantom studies are required for PET imaging of small liver tumors using pure ^{90}Y , as tumor diameter cannot be adequately characterized.

Before separation, ^{90}Y -labeled microspheres contain a partially cross-linked cation-exchange polymer matrix composed of polystyrene resin. During labeling, $^{90}\text{Y}^{3+}$ replaces sodium ions (Na^+) via ion exchange and binds to the resin matrix, thereby attaching to the microspheres. Subsequently, ^{90}Y is immobilized on the microspheres by precipitation in the form of a phosphate salt. The ^{90}Y -microsphere complex is maintained together by physical forces rather than chemical bonds, resulting in a relatively weak association that may be disrupted in highly ionic environments. SIR-Spheres consist of biocompatible resin microspheres radiolabeled with ^{90}Y . During ion exchange, sodium ions (Na^+) are replaced by $^{90}\text{Y}^{3+}$, which binds to the polystyrene cation-exchange resin layer. Subsequently, ^{90}Y is immobilized on the resin microspheres by phosphate precipitation (17).

Although previous phantom studies have used ^{90}Y chloride solutions, studies investigating the extraction of ^{90}Y from commercial resin microspheres and its subsequent use in phantom imaging are extremely limited. The ability to obtain a homogeneous ionic ^{90}Y solution from microspheres may provide a significant advantage for cost-effective phantom-based dosimetric research and imaging studies. The aim of this study is to separate ^{90}Y from microspheres into ionic form, optimize the preparation of ^{90}Y solution for experimental studies, and validate its accuracy using PET/CT imaging and quantitative analysis.

Material and Methods

No live data were used in this study, and all data were produced from phantom studies. Due to the harmful effects of radiation on living organisms, experimental studies involving radiation are often conducted using organ-mimicking phantoms. In this study, we used a phantom resembling the human liver, containing two simulated tumors with known volumes. The study was planned in two stages: the first stage involved filtration of solutions with microspheres, and the second stage involved imaging and quantification of the phantom using PET/CT. The imaging was performed both when the phantom was

labeled with microspheres and after the microspheres were separated from the ⁹⁰Y.

⁹⁰Y Microspheres Characteristics and Separation Technique

Commercially available resin-based ⁹⁰Y microspheres were used as the radionuclide source in this study. The microspheres consist of a polystyrene resin matrix with an average diameter of $32 \pm 10 \mu\text{m}$ and a specific gravity of approximately 1.6 g/dL (15,16). The association between ⁹⁰Y and the resin matrix can be disrupted under highly ionic conditions, allowing the radionuclide to be separated from the microspheres. To separate the ⁹⁰Y isotope from this resin, the microspheres were treated with a solution composed of a mixture of 5.5 M NaCl and 6 M HCl at pH 5 [NaCl (pKa: 7.15), HCl (pKa: -6.3), and Y+3 (pKa: 10.64)]. After incubation at room temperature for 2 hours, the solution containing ionic ⁹⁰Y was separated from the resin particles by passing it through a $0.22 \mu\text{m}$ PTFE filter. Since the initial trial was successful, further experimental replication was not performed. The microspheres within the ⁹⁰Y complex have dimensions ranging from 20 to 60 microns (with an average of 32 ± 10 microns), which prevented them from passing through sterilizing filters due to their size. Consequently, when these microspheres were transferred into the product vial in their free form, they became trapped within the vial. Meanwhile, the ⁹⁰Y radionuclide remained in its free form within the product vial, completing the separation process. The separated ionic form of ⁹⁰Y radionuclide was then utilized in the second phase of phantom imaging studies.

Liver Phantom and Water Tank

The liver model used in this study consists of three main sections: normal liver tissue, a large tumor, and a small tumor. Collaboration with the chemical engineering department was employed to determine the materials for the phantom. The liver phantom was fabricated from filament material called polylactic acid using fused deposition modeling on 3D printers. The model was designed to have a specific gravity similar to human tissue ($d=1.24 \text{ g/cm}^3$). The dimensions of the liver phantom are 112 mm x 191 mm with an empty mass of 350 grams, and it includes three caps for filling with radiopharmaceutical solution.

The leftmost cap is used to fill the 690 cm^3 volume representing the hepatic parenchyma (normal liver) with liquid radioactive material. The other caps, designed as cylindrical structures with volumes of 9.5 cm^3 and 202 cm^3 respectively, are used to fill liquid radioactive material into two separate and independently designed tumors

of different sizes (Figure 1). These tumor sizes represent commonly encountered small and relatively large volumes. Scintigraphic imaging of the liver phantom was conducted using a tank made of plexiglass that matches the dimensions of a normal human abdominal area and can be filled with water.

Measurement of ⁹⁰Y Radioactivity, Imaging Protocol and Quantification

Radioactivity measurements were performed using a dose calibrator (Biodex Atom lab 300 dose calibrator). Accuracy tests of the dose calibrator were performed with a Cs-137 calibration source prior to measurement. The activities of ⁹⁰Y in ionic form, to be injected into the simulated tumors and empty spaces representing normal liver tissue in the phantom, were drawn into syringes and measured in the dose calibrator. Subsequently, the ⁹⁰Y radionuclide was diluted with water, and activities of 684 MBq, 2025 MBq, and 18.70 MBq were respectively filled into the locations representing normal liver, large tumor, and small tumor in the phantom. Empty syringes were measured again for background correction. This process allowed the determination of the net activity amounts deposited into the phantoms.

The PET/CT images of the phantom were acquired using a Siemens Horizon Biograph model scanner with the subject positioned on a single bed for a duration of 20



Figure 1. View of the liver phantom inside the water tank. The figure shows the liver phantom placed inside a water tank. The filling caps, from left to right, correspond to the normal liver, small tumor, and large tumor compartments, respectively

minutes. The imaging process was carried out in two stages: in the initial stage, imaging was performed using the radiopharmaceutical labeled with ^{90}Y microspheres. In the second stage, following separation from the ^{90}Y microspheres, the phantom was filled with the microspheres, and imaging was repeated under identical conditions using the same PET/CT scanner.

The image reconstruction was performed according to routine clinical protocol using the OSEM 3D algorithm with 16 subsets and 8 iterations. Quantification PET/CT images was carried out using the OsiriX Dicam Viewer program. In the first stage, after filling the phantom with a solution of ^{90}Y microspheres into the tumor-simulating regions and empty spaces representing normal liver tissue, PET/CT imaging

was performed. The PET images showed the settling of ^{90}Y microspheres towards the bottom. Volumes of interest (VOIs) were drawn around the areas where microspheres settled and named as VOI_1 and VOI_2 . in accordance with conventional use. Similarly, the entire liver (including tumors) was named VOI_3 (Figure 2). Subsequently, the counts for $\text{VOI}_3 - (\text{VOI}_1 + \text{VOI}_2)$ were calculated to determine the ratio of settled ^{90}Y microspheres. The ratio of settled ^{90}Y microspheres $[(\text{VOI}_1 + \text{VOI}_2) / \text{VOI}_3]$ was determined using the equation.

In the second stage, the actual values of the ^{90}Y activity per unit volume (MBq/mL) for normal liver (N) and tumor (T) were calculated based on the amounts of ^{90}Y activity filled into the phantom. PET images were used to draw 10 VOIs of the same size over the normal liver and separately over the tumors to determine the counts.

Statistical Analysis

The T/N ratios in the ^{90}Y microsphere PET/CT images and the T/N ratios in the ^{90}Y PET/CT images were evaluated using the Mann-Whitney U test. A significance level of $p < 0.05$ was used to indicate a statistically significant difference.

Results

After filling the phantom with the solution of ^{90}Y microspheres into the tumor-simulating regions and empty spaces representing normal liver tissue, PET/CT imaging was conducted. VOIs were drawn around the areas where microspheres settled. These regions were named VOI_1 and VOI_2 , and their total counts were determined (Figure 2). The total count for VOI_1 was 82484 and for VOI_2 it was 62039. The total count for the entire liver (including tumors) was determined by drawing the VOI around the area of interest, resulting in a count of 151204 for VOI_3 . Using these counts, the ratio of settled microspheres $[(\text{VOI}_1 + \text{VOI}_2) / \text{VOI}_3]$ was calculated as $(82484 + 62039) / 151204 = 0.95858$ (95.58%).

The actual ^{90}Y unit activity amounts Mega Becquerel/cm³ (MBq/cm³) placed into the phantom were 1 MBq/cm³ for normal liver (N), 9.9 MBq/cm³ for the large tumor (Ltm), and 4.73 MBq/cm³ for the small tumor (Stm), considering the volumes of the tumors. The T/N ratios for Ltm and Stm were determined to be 1/10 and 1/2, respectively. After separating the microspheres and filling pure ^{90}Y into the phantom and tumor-simulating regions, PET/CT imaging was performed. The obtained images showed that the ^{90}Y microspheres did not settle at the bottom but distributed relatively homogeneously. VOIs were drawn around the outer boundaries of the tumors on the images. The large and small tumors were labeled as Ltm and

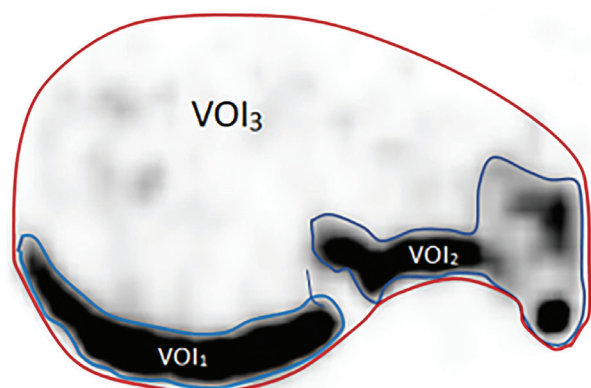


Figure 2. VOIs drawn on the PET/CT Image of ^{90}Y microspheres filled in the phantom. VOIs were delineated on the PET/CT image of the phantom filled with ^{90}Y
VOI: Volume of interest, PET/CT: Positron emission tomography/computed tomography, ^{90}Y : Yttrium-90

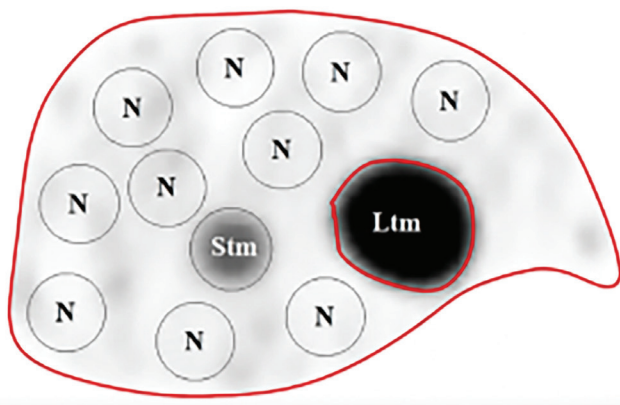


Figure 3. VOIs Drawn on the PET/CT Image of ^{90}Y Filled in the Phantom. VOIs were delineated on the PET/CT image of the phantom filled with ^{90}Y
VOI: Volume of interest, PET/CT: Positron Emission tomography/computed tomography, ^{90}Y : Yttrium-90; Ltm: Large tumor, Stm: Small tumor, N: Normal liver

Stm, respectively. Additionally, 10 VOIs were drawn from different regions corresponding to normal liver tissue (N) on the cross-sectional image (Figure 3). The average VOI counts were 70120 for Ltm and 13848 for Stm. The T/N ratios were calculated by dividing the average VOI counts of Stm and Ltm by the VOI counts of N separately (Table 1).

Data distribution was assessed and non-parametric statistics were therefore applied. Statistical Comparison of Ltm and Stm T/N Values Using Mann-Whitney U Test Revealed a Highly Significant Difference at the $p=0.00018$ Level.

Discussion

The present study demonstrated that ⁹⁰Y can be successfully separated from commercially available resin microspheres and converted into an ionic solution suitable for phantom-based PET/CT imaging studies. When the separated ionic ⁹⁰Y solution was introduced into the phantom, it exhibited a homogeneous distribution, thereby enabling reliable quantitative PET analysis.

The differences between the two preparation methods before and after separation of the particulate resin microspheres were demonstrated both visually and quantitatively in Figures 2 and 3. Approximately 95.6% of the detected activity from the intact microspheres accumulated in the dependent (lower) regions of the phantom, confirming that gravitational sedimentation dominates the distribution of resin microspheres under static phantom conditions. Such sedimentation renders phantom studies unsuitable for quantitative imaging

and dosimetric validation because the intended activity distribution cannot be maintained. In contrast, following separation of ⁹⁰Y from the microspheres, the activity was distributed throughout the phantom without visible sedimentation, resulting in PET images that more accurately reflected the intended activity concentrations.

An important finding of this study was the close agreement between the prepared activity concentrations and the quantitative measurements obtained from PET imaging. The planned tumor-to-normal liver (T/N) activity concentration ratio was 10:1 for the large tumor and 2:1 for the small tumor. PET imaging yielded mean T/N ratios of 11.3 ± 0.8 and 2.26 ± 0.17 , respectively. Although minor deviations were observed, these differences were within the expected range attributable to the PVE, the spatial resolution of PET, image reconstruction, VOI delineation, and counting statistics. Furthermore, the Mann-Whitney U test demonstrated a highly significant difference between the T/N ratios of the two tumor models ($p=0.00018$). These findings confirm that the prepared phantom successfully generated two distinct activity concentrations that were quantitatively distinguishable by PET/CT.

Most phantom studies reported in the literature have used commercially available ⁹⁰Y chloride (⁹⁰YCl₃) solutions because of their inherently homogeneous distribution (15). Son et al. (18) used ⁹⁰Y chloride in a phantom dosimetry study and demonstrated that its homogeneous activity distribution was suitable for quantitative PET imaging. Similarly, Mille et al. (19) performed phantom experiments using a homogeneous ⁹⁰YCl₃ solution. They emphasized the usefulness of this approach for image-based dosimetry while also recommending that future studies investigate more realistic heterogeneous activity distributions. In contrast, the present study demonstrates that by separating ionic ⁹⁰Y from residual resin microspheres obtained from clinical applications, a homogeneous mixture exceeding 95% uniformity can be achieved for phantom studies. This approach therefore provides an alternative radionuclide source for phantom preparation without requiring commercially available ⁹⁰Y chloride.

Clinical studies have shown that ⁹⁰Y resin microspheres do not sediment under the influence of gravity but instead become distributed throughout the hepatic arterial microvasculature. Gulec et al. (11) reported consistent tumor-to-normal liver uptake ratios following radioembolization, demonstrating that the microspheres become physiologically embolized within the hepatic arterioles. Likewise, Son et al. (18) reported good agreement between dosimetric estimates obtained using ^{99m}Tc-MAA single photon emission computed tomography (SPECT)/CT and post-treatment

Table 1. T/N ratios calculated from VOIs drawn on the PET/CT image showing relatively homogeneous distribution of ⁹⁰Y in the phantom

N	VOI (Counts)	T/N (Stm)	T/N (Ltm)
1	6623	2.09	10.6
2	6568	2.10	10.7
3	6459	2.14	10.9
4	6123	2.26	11.5
5	6425	2.16	10.9
6	5523	2.50	12.7
7	6610	2.10	10.6
8	5423	2.54	12.9
9	5887	2.34	11.9
10	5968	2.32	11.7
Mean $\pm$ SD	6203 $\pm$ 447	2.26 $\pm$ 0.17	11.3 $\pm$ 0.8

T/N: Tumor-to-normal tissue ratio, VOI: Volume of interest, PET/CT: Positron emission tomography/computed tomography, ⁹⁰Y: Yttrium-90, SD: Standard deviation, Stm: Small tumor, Ltm: Large tumor

⁹⁰Y PET/CT findings. Furthermore, Elschot et al. (20) demonstrated that PET/CT provides more accurate post-treatment activity quantification than Bremsstrahlung SPECT imaging. These clinical observations fundamentally differ from static phantom experiments because, under in vivo conditions, the microspheres are retained within the tumor microvasculature rather than freely settling under gravity. Consequently, the sedimentation observed in our initial phantom experiment should not be interpreted as a limitation of clinical radioembolization but rather as a phenomenon specific to the static phantom model. For phantom applications requiring homogeneous activity distribution, separation of ⁹⁰Y from the microspheres therefore appears to be necessary.

Although the separated ionic solution produced a substantially more homogeneous activity distribution, minor count differences were still observed among the VOIs representing N tissue (Table 1). These small variations are more likely attributable to the intrinsic characteristics of PET imaging, including image noise, positron range, limited spatial resolution, and VOI placement, rather than incomplete mixing of the radionuclide. In addition, because image acquisition and reconstruction were performed using a routine clinical PET/CT protocol, no recovery coefficient or partial volume correction was applied, ensuring that the results reflected standard clinical imaging conditions.

Study Limitations

This study has several limitations. First, only a single separation protocol employing a 0.22 µm sterile membrane filter was evaluated, and alternative separation techniques were not investigated. Second, only PET/CT imaging was assessed, whereas other quantitative imaging modalities, such as SPECT/CT, were not examined. Finally, the experiments were performed using a static phantom, which cannot fully reproduce the complex vascular trapping mechanisms and heterogeneous microsphere distribution encountered during clinical radioembolization. Future studies should evaluate alternative separation methods, different phantom geometries, and multimodal imaging approaches to provide a more comprehensive validation of this technique.

Conclusion

In conclusion, when used under static phantom conditions, ⁹⁰Y resin microspheres tend to sediment because of their particulate nature and higher density. To achieve a homogeneous distribution of ⁹⁰Y in any medium, appears to be necessary for phantom studies requiring homogeneous activity distribution. In this study, it was demonstrated that

ionic ⁹⁰Y radionuclide can be successfully obtained from ⁹⁰Y resin microspheres by filtration through a sterile 0.22 µm membrane filter (Merck Millipore).

Ethics

Ethics Committee Approval: Since it is not a live study, ethics committee approval is not required.

Informed Consent: N/A.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Author Contributions: Concept: Ö.D., E.K., Design: Ö.D., Data Collection or Processing: Ö.D., E.K., Analysis or Interpretation: Ö.D., E.K., Literature Search: Ö.D., E.K.; Writing: Ö.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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